REMARKS

Status of the Claims

Claims 1, 3-70, 72, 75-77 and 138-142 are under examination. Claims 1, 3-68, 75 and 138-141 are rejected. Claims 69, 70, 72, 76, 77 and 142 are allowed. Claims 2, 71, 73, 74 and 78-137 were previously canceled. Claims 1, 68, 140, and 141 are amended.

Claim Amendments

Claim 1 has been amended by deleting the phrase "expressed on the plasma membrane of a cell surface" from the preamble. Applicants note that step (b) of claim 1 provides support for expression of the transport protein on the plasma membrane of the cell surface: "one or more of the cells expressing one or more carrier-mediated transport proteins on the plasma membrane of the cell surface."

Claims 68 and 140 are amended to consistently recite "carrier-mediated transport protein". Support for these amendments can be found, for example, on page 9, lines 17-21 of the originally filed specification.

Claim 141 is amended by replacing "the population of cells" in the second to last line with "the cell" to establish proper antecedent basis.

Thus, the amendments to the claims are fully supported by the specification as originally filed and add no new matter.

Claim Rejections – 35 U.S.C. § 112, second paragraph

5.A. The Examiner rejects claim 68 and all dependent claims under 35 U.S.C. § 112, second paragraph as being vague and indefinite in the use of the word "type" in the phrase "carrier-type." Applicants have amended claim 68 by replacing the phrase "carrier-type" with "carrier-mediated" thereby addressing the Examiner's rejection.

5.B. The Examiner rejects claim 1 and all dependent claims as lacking antecedent basis for the element "the plasma membrane of the cell surface." Applicants have deleted the phrase

from the preamble, thereby addressing the Examiner's rejection. "[A] plasma membrane" and a "carrier-mediated transport protein" expressed on the plasma membrane of the cell surface are properly introduced in step (b) of the claim.

In view of the foregoing, Applicants respectfully request withdrawal of the rejections of claims 1 and 68 and the corresponding dependent claims under 35 U.S.C. § 112, second paragraph.

Claim Rejections – 35 U.S.C. § 102

An anticipatory reference under 35 U.S.C. § 102 must disclose each limitation of the claims (*M.P.E.P.* § 2131, Rev. 5. August 2006, p. 2100-67; *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628 (Fed. Cir. 1987) ("A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.").

7. The Examiner rejects claim 75 under 35 U.S.C. § 102(b) as being anticipated by Swanson *et al.* as evidenced by Ozkan *et al.* The Examiner alleges that Swanson *et al.* disclose, in pertinent part, (a) providing a library comprising different complexes, each complex comprising a compound and a separate report, and (c) contacting the plurality of different cells with a plurality of complexes from the library simultaneously. Applicants respectfully traverse.

Swanson *et al.* disclose contacting aleurone protoplasts with the protease substrate ZFR-CMAC. Upon entering the aleurone protoplast cyctoplasm, ZFR-CMAC is conjugated to glutathione (SG) to produce the complex ZFR-CMAC-SG. The complex is translocated into secondary vacuoles and into protein storage vacuoles where the complex undergoes proteolysis to generate the fluorescent product of ZFR-CMAC-SG, NH_2-CMAC-SG (see Figure 4). ZFR-CMAC is a nonfluorescent compound that releases fluorescent CMAC when the peptide bond between the CMAC fluorophore and the adjacent ZFR arginine residue is cleaved (page 688, col. 1, lines 5-12). The covalent addition of glutathione to the ZFR-CMAC molecule leads to ATP-dependent transport of the CMAC fluorophore into vacuoles, whereas vacuoles incubated with ZFR-CMAC do not accumulate CMAC (page 688, col. 2, lines 15-26; and Figure 5).

In step (a), claim 75 recites "a library comprising different complexes, each complex comprising a compound and a separate reporter, the compound varying between different complexes." Reporters are molecules that are capable of generating a detectable signal (page 4, lines 7-8) such as an optical signal (page 13, lines 25-29). Reporters can be conditional reporters in which the signal is not generated (or at least not substantially generated) until the reporter is internalized within the cell (page 4, lines 16-20).

As characterized by Swanson *et al.*, CMAC is the fluorophore, and hence in Applicants' terms, a reporter. Swanson *et al.* does not disclose or suggest that Cl, or any other atom or moiety of the CMAC fluorophore, are independent entities such that CMAC is to be considered a complex. The Examiner impermissibly advances an artificial distinction that is not present in the prior art (*see, e.g.*, *Structural Rubber Prods. Co. v. Park Rubber Co.*, 749 F.2d 707, 716 (Fed. Cir. 1984) (Missing elements may not be supplied by the knowledge of one skilled in the art or the disclosure of another reference); and *Minnesota Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559, 1572 (Fed. Cir. 1992) (The reference must, however, "sufficiently describe the clamed invention to have placed the public in possession of it.")). Thus, it is the CMAC molecule that is the fluorophore or reporter, and not CMAC less the chlorine atom.

ZFR-CMAC is an example of a conditional reporter because in the presence of an intracellular protease, it is proteolyzed to generate the fluorescent CMAC probe. On the other hand, ZFR-CMAC-SG is an example of a complex comprising both a conditional reporter (ZFR-CMAC) and a compound (glutathione). Accordingly, in Figure 4 and throughout, Swanson *et al.* discloses contacting vacuoles with a reporter and a *single* reporter-compound complex. Swanson *et al.* does not disclose or suggest a library of complexes as those terms are used by Applicants.

Alternatively, the Examiner proposes parsing CMAC (7-amino-4-chloromethylcoumarin) such that the fluorophore is considered a complex comprising the reporter 7-amino-4-methylcoumarin (CMAC less the chlorine substituent) and the "compound" Cl. As previously stated, Swanson *et al.* does not disclose reconstructing the fluorophore CMAC into

subcomponents. However, assuming *arguendo*, the Examiner's characterization, Swanson *et al.* would still not be anticipatory.

ZFR-CMAC(-Cl) and ZFR-CMAC-SG differ in that a chlorine group is replaced with glutathione. The Examiner alleges that with respect to Applicants' claimed method Cl and SG represent different compounds and ZFR-CMAC is the reporter. (Although the Examiner alleges that the moieties $-CH_2Cl$ and $-CH_2SG$ represent different compounds, this characterization is inaccurate.) The Examiner is incorrect in characterizing Cl as a compound. "A chemical compound is a substance consisting of two or more elements chemically bonded together in a fixed proportion by mass (see e.g., definition in Wikipedia). Accordingly, Cl is properly characterized as an element while SG is properly characterized as a compound. Hence, ZFR-CMAC(-Cl) is a complex comprising an element (Cl) and a reporter (ZFR-CMAC), and ZFR-CMAC-SG is a complex comprising a compound (SG) and the same reporter (ZFR-CMAC).

Applicants claim, in pertinent part, (a) providing a library comprising different complexes, each complex comprising a compound and a separate reporter, the compound varying between different complexes; and (c) contacting the plurality of different cells with a plurality of complexes from the library simultaneously. As set forth above, Swanson *et al.* disclose only a single complex comprising a compound and a separate reporter, and not a library comprising complexes comprising a compound and a separate reporter. Therefore, Swanson *et al.* do not disclose each element recited in steps (a) and (c) of claim 75. Because Swanson *et al.* do not disclose each element recited in Applicants' claim 75, Swanson *et al.* cannot anticipate the claim.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection of claim 75 under 35 U.S.C. § 102(b) as anticipated by Swanson *et al.*

Claim Rejections – 35 U.S.C. § 112, second paragraph

9.A. The Examiner rejects claim 140 under 35 U.S.C. § 112, second paragraph as being indefinite in the use of the word "type" in the phrase "carrier-type. Applicants have

amended claim 140 by replacing the phrase "carrier-type" with "carrier-mediated" thereby addressing the Examiner's rejection.

9.B. The Examiner rejects claim 141 under 35 U.S.C. § 112, second paragraph as having insufficient basis for the element "the population of cells" in the second to last line. Applicants have amended claim 141 by replacing the phrase "the population of cells" in the second to last line with the phrase "the cell" thereby establishing antecedent basis and addressing the Examiner's rejection.

In view of the foregoing, Applicants respectfully request withdrawal of the rejections of claims 140 and 141 under 35 U.S.C. § 112, second paragraph

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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